med WATCH

How to OUTSMART Cancer

TUMOR TALK: Doctors now look differently at genetic codes to help prevent disease, individually.

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Beyond genes and genomics, scientists are now tracking tiny proteins that spur tumors to grow. This is where personalized medicine meets "proteomics." And as new diagnostic tests appear, one thing's for certain: Genes don't tell the whole survivor story. Not even close.

BY MARY ELLEN HANNIBAL

IN CANCER SLEUTHING, ONE OF THE MODERN MANTRAS is early detection. For in most cancer categories, survival rates improve dramatically when the disease is diagnosed early and confined to the organ of origin. Five-year survival rates for colon, ovarian, lung, breast, and prostate cancers are better by orders of magnitude when treatment begins at the get-go. But finding them when they're young often is easier said than done. When diagnosed early, certain types of ovarian cancer cases, for example, have a 90 percent survival rate at five years—but nearly two-thirds of ovarian cancer diagnoses are made only after it has spread, according to the National Institutes of Health (NIH). And then the five-year survival rate plummets to 28 percent.

Today, the cancer brain trust drilling down on this problem is changing the game—and aiming to improve the odds markedly. Researchers in government, industry, and academia are all talking about simple, powerful blood tests coming down the pike, beyond genetic tests, in which nascent cancers will be able to be detected early, when effects of treatment are most promising.

Well, it's simple enough to draw blood. What happens after that is a bit more complex. Doctors already use several blood tests to screen for cancer. The trouble is, they aren't very accurate. Basically these tests look for tiny proteins (or biomarkers) associated with different cancers. Yet, as one example, the protein-based CA-125 blood test detects ovarian cancer only about 50 percent of the time (this is called low *sensitivity*), and often alarmingly flags unrelated conditions such as endometriosis and pregnancy—meaning the test has low *specificity*. The CEA test used to track colorectal cancer, which measures levels of carcino-embryonic antigen (a protein), is currently so variable that only selected survivors who are facing or have had surgery are recommended to use it. In men, the prostate-specific antigen (PSA, a protein) that's used to hunt down prostate cancer also receives low marks. Only 44 percent of men who have biopsies due to high PSA turn out to have cancer. And the test misses flagging up to 56 percent of men who do have the disease, doctors reported in 2009 in the *British Medical Journal*. Similarly, more than 50 percent of all lung cancer cases are detected after the disease has spread, and these diagnoses carry a dismal 4 percent chance of five-year survival, the NIH says.

"At the highest level of the early detection technologies, people are trying to find things that are unique and specific to cancer," explains Don Listwin, founder and chairman of the Canary Foundation, a cancer-based research group in Palo Alto, Calif. Listwin is a technology guru: Among many other achievements he was the number two executive at Cisco Systems. His Canary Foundation works to link various cancer research efforts that ordinarily operate in their own silos—much the way he helped assemble separate technologies that together made the Internet possible—and develop a fuller vision for early detection based on multiple disciplines.

"We find proxies and stuff associated with cancer, like PSA," he says. "I have [measurable levels of] PSA right now, even though I don't have cancer. We are trying to find markers that are 100 percent specific to cancer."

A valuable place to look for cancer markers, cancer researchers now say, isn't just in the genome, but the *proteome*, a different biological target. "Understanding the biology of the tumor can lead to better, more effective treatment," says Mark G. Kris, M.D., of Memorial Sloan-Kettering Cancer Center (a LIVE**STRONG** Survivorship Center of Excellence), who recently shared findings with colleagues about pinpointing lung cancer survivors for a potential new benefit. And the burgeoning field of proteomics is being embraced big-time by the government, through the National Cancer Institute; academic ventures like the Canary Center at Stanford for Cancer Early Detection, which collaborates with Stanford University's Comprehensive Cancer Center; and biotech firms in private industry, including a small, Boulder, Colo., startup called SomaLogic.

So, what is this proteome? We all know about the human genome, the DNA blueprint each of us is endowed with from the very moment of our conception, with genetic contributions half from our mother and half from our father. Our genome stays pretty much steady state throughout our entire lifespan—the biologic sum total of the raw materials we inherited. The genome holds the code to produce proteins, and these abundant little components drive the workings of all our cells, tissues, and organs. Each of us has approximately 20,000–25,000 protein-coding genes, which produce up to a million proteins over the course of a lifetime.

Despite the excitement, **HIGHLY TARGETED BLOOD TESTS** to detect cancer still face milestones before moving into clinical practice.

In turn, the whole protein kit and caboodle, the entirety of all the proteins that make up a single person, is the proteome. In contrast to the genome, the proteome changes constantly, responding to diet, exercise, sleep patterns, pollution, and the aging process. While the genome is used to predict disease based on your family history, the proteome is the source for determining whether you actually *have* it, because it changes when disease is present.

In order to boost the lagging efficacy of the blood tests we currently use, SomaLogic is developing what the company calls precision medicine: Instead of searching for one protein that may indicate disease, their diagnostic technology searches for many. "We don't have to live with the performance of a single test," says Steve Williams, M.D., SomaLogic's chief medical officer. In theory, the much higher accuracy of these tests may mean patients and survivors will undergo far fewer unnecessary biopsies and radiation exposures from imaging. At the same time, the number of false positive tests for cancer is expected to drop markedly.

Larry Gold, Ph.D., founder and CEO of SomaLogic, and professor of biology at the University of Colorado, puts it this way: "If measuring one thing tells you something, then measuring more stuff tells you more. We measure over 1,000 features in one drop of blood." The proteome offers, potentially, a mother lode of personalized health information, far beyond predicting cancer or cancer recurrence risk, SomaLogic and other scientists say. Similar tests can be developed to ferret out diseases such as Alzheimer's and Parkinson's.

In clinical trials, recent results quoted by SomaLogic include an impressive 90 percent sensitivity for confirming Stage I lung cancer—meaning the test identified or "got it right" most of the time. Likewise, the firm's mesothelioma (asbestos-related) trial was 92 percent accurate in finding or confirming Stage I disease. These tests, and others developed by competitor Pacific BioSciences in California, could well prove far superior to available tests and scans, which is probably why firms like Quest Diagnostics, NEC in Japan, and Otsuka Pharmaceutical already have invested hundreds of millions of dollars in small firms like SomaLogic.

And what's going on over at the Canary Center at Stanford ("canary" for the coal mine allusion) may be even more comprehensive and exciting. As Listwin says, "Nobody goes from screening to scalpel"—meaning there's more work to be done; even after these new blood tests become available. "We'll need molecular imaging to confirm and isolate the finding." One such imaging test is already in trials. The molecular sleuth under study has three elements: a homing agent, a linking agent, and a tiny light bulb, essentially. Together, these link to an antibody (the target) and illuminate it for the camera—the molecular imaging. In November, the FDA approved Canary's "exploratory investigational new drug" for testing molecular imaging agents that can detect tumors in early lung cancer. Listwin estimates that by 2016, Canary will have diagnostics and technology for oncologists working with the highest-risk patients. His goal, he says, is "to get an industry created and shut ourselves down."

Despite the excitement inherent in this research, the concept of highly targeted blood tests to detect cancer still faces considerable milestones before moving into clinical practice. "Part of the reason it's hard to know how screening tests will evolve in the clinic can be gleaned from the difficulty we have knowing exactly how to use the tests we already have," says Brandon Hayes-Lattin, M.D., medical director of the Adolescent and Young Adult Oncology Program at Oregon Health & Science University's Knight Cancer Institute.

"The tests are going to find cancer at very early stages, although some cancers found may never have turned life-threatening. The medical field doesn't yet know how to handle all these results," adds Dr. Hayes-Lattin, a testicular cancer survivor and senior medical advisor to LIVE**STRONG**. Speaking about prostate cancer, Hayes-Lattin points out that many men walking around with the disease in their bodies are unaware of the fact; and they are no worse for not knowing. "They will die of something else. It wouldn't be clinically relevant to treat their cancer."

Yet, at the June annual meeting of the American Society for Clinical Oncology, "molecular profiling," plus a brand-new model for detecting a gene mutation that is found in about 50 percent of all melanomas, both made big news. It's a start. "This science is discovering what's molecularly broken," Hayes-Lattin explains. "Then, instead of hitting the patient with a hammer, you can target what's broken with relatively few side effects." ■

*For clinical trials that involve new diagnostics or proteomics, visit ClinicalTrials.gov or LIVE**STRONG**.org/GetHelp.*

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